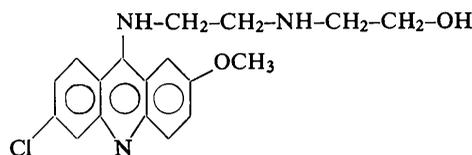


The Crystal Structure of 2-[2-(6-Chloro-2-methoxy-9-acridinylamino)ethylamino] ethanol(ICR-171-OH)

BY JENNY PICKWORTH GLUSKER, JEAN A. MINKIN* AND WALTER OREHOWSKY, JR
The Institute for Cancer Research, Philadelphia, Pennsylvania 19111, U.S.A.

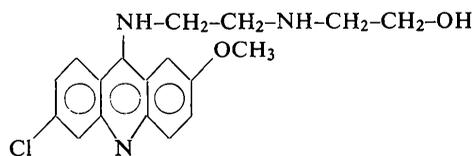
(Received 29 December 1970)

The crystal structure of 2-[2-(6-chloro-2-methoxy-9-acridinylamino)ethylamino]ethanol, the hydroxy-precursor (ICR-171-OH) of a mutagenic acridine nitrogen half-mustard, has been studied. It crystallizes in the space group $P2_1/a$ with $Z=4$, cell dimensions $a=23.027 \pm 0.012$, $b=7.676 \pm 0.004$, $c=9.923 \pm 0.006$ Å, $\beta=100.12 \pm 0.10^\circ$. The observed and calculated densities are 1.30 and 1.31 g.cm⁻³ respectively. The compound has the formula



Data were collected on a manual diffractometer with Cu $K\alpha$ radiation. 2148 out of 3753 reflections scanned were above the threshold of measurement. The structure was solved by the symbolic addition procedure and refined by least-squares methods to an R value of 0.066. The analysis shows that the acridine portion of the molecule is not planar, the buckling being not simply a folding of the molecule but corresponding to an angle of 7.4° between the planes of the two outer rings. These outer rings are each planar within experimental error. There is an intramolecular hydrogen bond between the two nitrogen atoms of the side chain and two intermolecular hydrogen bonds involving the terminal hydroxyl group with the ring nitrogen atom and with a side chain nitrogen atom.

This structure determination is part of a proposed series of studies of acridine and anthracene nitrogen and sulphur mustards possessing antitumor or mutagenic properties. The compound under investigation, referred to as ICR-171-OH, is the precursor ($-\text{CH}_2-\text{CH}_2-\text{OH}$ replacing $-\text{CH}_2-\text{CH}_2-\text{Cl}$ in the side chain of the mustard) of a compound, ICR-171 (Peck, Preston & Creech, 1961), which is a mutagen for *Salmonella* but not an active antitumor agent. The chemical formula is shown below:



The precursor was studied because crystals suitable for an X-ray structure determination were readily obtained. Crystallization has not, so far, been possible with the mustard itself.

Experimental

Very fine bright yellow needles were grown by keeping a solution of ICR-171-OH in a 4:1 ethanol-water

* Present address: U.S. Geological Survey, Washington, D.C. 20242, U.S.A.

mixture at 40°C for several days and then leaving it at room temperature to evaporate.

Cell dimensions were measured from precession photographs and on a manual diffractometer with copper $K\alpha$ radiation [$\lambda(K\alpha_1)=1.5405$ Å]. The dimensions of the monoclinic cell are $a=23.027 \pm 0.012$, $b=7.676 \pm 0.004$, $c=9.923 \pm 0.006$ Å, $\beta=100.12 \pm 0.10^\circ$. The space group (determined from systematic absences $h0l$ with h odd and $0k0$ with k odd) is $P2_1/a$. The density, measured by flotation in potassium iodide solution, is 1.30 g.cm⁻³, while that calculated for four molecules of $\text{ClO}_2\text{N}_3\text{C}_{18}\text{H}_{14}$ (F.W. 339.79) is 1.31 g.cm⁻³.

Three-dimensional data were collected on a crystal of dimensions $0.09 \times 0.16 \times 0.39$ mm. The crystal was small, the largest that we were able to grow, and only 57% of the reflections, 2146 out of 3749 scanned, were above the threshold of measurement. There were observed reflections throughout the entire range of 2θ to 160° . Data were collected on a General Electric XRD-5 diffractometer with nickel-filtered copper radiation with the $\theta-2\theta$ scan technique. They were corrected for Lorentz and polarization factors and absorption factors ($\mu=23.14$ cm⁻¹).

Determination of the structure

The structure was determined by the symbolic addition procedure with assistance from Fourier maps. Approx-

Table 1. *Final parameters of atoms*

Positional parameters of non-hydrogen atoms are expressed as fractions of cell edges $\times 10^4$. Anisotropic temperature factors are expressed as:

$$\exp(-b_{11}h^2 - b_{22}k^2 - b_{33}l^2 - b_{12}hk - b_{23}kl - b_{13}hl) \times 10^4.$$

Estimated standard deviations, determined from the inverted full matrices, are listed in parentheses beside each parameter with respect to the last decimal place given.

	<i>x</i>	<i>y</i>	<i>z</i>	<i>b</i> ₁₁	<i>b</i> ₂₂	<i>b</i> ₃₃	<i>b</i> ₁₂	<i>b</i> ₁₃	<i>b</i> ₂₃
Cl(1)	357 (1)	7141 (2)	1112 (1)	19.5 (2)	439 (4)	111 (1)	-1 (2)	-30 (1)	12 (5)
O(2)	3345 (1)	7092 (4)	10191 (2)	18.7 (6)	394 (10)	72 (3)	1 (4)	-10 (2)	41 (10)
O(3)	5445 (1)	5673 (4)	6690 (3)	14.4 (5)	220 (7)	116 (3)	-1 (3)	21 (2)	-53 (9)
N(4)	1454 (1)	7832 (4)	5949 (3)	12.1 (5)	183 (8)	85 (3)	5 (4)	12 (2)	15 (10)
N(5)	3113 (1)	6741 (5)	4927 (3)	13.9 (6)	300 (10)	79 (3)	45 (4)	15 (2)	45 (11)
N(6)	4305 (1)	7120 (4)	5350 (3)	14.2 (6)	170 (8)	109 (4)	9 (4)	5 (2)	-29 (10)
C(7)	2991 (1)	6920 (6)	7738 (4)	12.5 (6)	203 (11)	85 (4)	10 (5)	13 (3)	6 (12)
C(8)	2913 (1)	7230 (6)	9051 (3)	15.1 (7)	272 (13)	72 (4)	-8 (5)	-4 (3)	23 (13)
C(9)	2360 (2)	7765 (7)	9328 (3)	19.0 (8)	335 (14)	66 (4)	-6 (6)	20 (3)	-21 (14)
C(10)	1889 (1)	7920 (6)	8299 (4)	14.9 (7)	264 (12)	90 (4)	-9 (5)	21 (3)	12 (14)
C(11)	983 (1)	7632 (6)	3632 (4)	11.6 (6)	197 (11)	101 (5)	-6 (5)	10 (3)	19 (12)
C(12)	1006 (1)	7113 (6)	2322 (4)	15.1 (7)	217 (11)	93 (4)	-14 (5)	-10 (3)	20 (13)
C(13)	1518 (2)	6553 (6)	1905 (3)	20.3 (9)	203 (11)	70 (4)	4 (5)	8 (3)	-19 (11)
C(14)	2032 (2)	6522 (6)	2831 (4)	16.0 (8)	206 (11)	80 (4)	10 (5)	11 (3)	-23 (11)
C(15)	2576 (1)	6977 (5)	5231 (3)	14.0 (7)	140 (9)	80 (4)	8 (5)	16 (3)	-1 (11)
C(16)	2508 (1)	7130 (5)	6625 (3)	12.2 (6)	137 (9)	75 (4)	-4 (4)	6 (2)	18 (11)
C(17)	1945 (1)	7603 (5)	6914 (3)	13.0 (6)	170 (10)	75 (4)	-10 (4)	15 (2)	9 (11)
C(18)	1510 (1)	7517 (5)	4640 (3)	13.1 (6)	117 (9)	85 (4)	-4 (4)	10 (3)	13 (10)
C(19)	2050 (1)	7046 (5)	4215 (3)	14.2 (6)	126 (9)	73 (4)	8 (4)	6 (2)	3 (11)
C(20)	3909 (2)	6541 (8)	10004 (4)	18.3 (9)	557 (20)	99 (5)	23 (7)	-8 (3)	82 (17)
C(21)	3361 (1)	7342 (5)	3754 (4)	16.3 (7)	171 (10)	93 (5)	26 (5)	16 (3)	16 (12)
C(22)	3952 (2)	8206 (6)	4278 (4)	20.0 (9)	171 (11)	145 (6)	3 (5)	4 (4)	32 (14)
C(23)	4761 (2)	8098 (6)	6263 (4)	19.4 (9)	191 (12)	156 (6)	-6 (6)	-5 (4)	-123 (15)
C(24)	5121 (2)	6920 (7)	7292 (4)	18.0 (8)	291 (14)	95 (5)	1 (6)	8 (3)	-80 (14)

Table 1 (cont.)

Parameters for hydrogen atoms. Positional parameters are multiplied by 10^3 .

Isotropic temperature factors are of the form $\exp(-B \sin^2\theta/\lambda^2)$ with *B* values given in \AA^2 .

Estimated standard deviations from the diagonal elements of the full matrix calculated for hydrogen atoms alone are

$$\sigma(x) = 0.007, \sigma(y) = 0.020, \sigma(z) = 0.015, \sigma(B) = 0.8 \text{ \AA}^2.$$

	<i>x</i>	<i>y</i>	<i>z</i>	<i>B</i>	attached to
H(25)	335	652	750	2.8	C(7)
H(26)	234	821	1025	5.4	C(9)
H(27)	153	833	857	7.5	C(10)
H(28)	61	803	391	5.1	C(11)
H(29)	153	606	100	6.6	C(13)
H(30)	237	622	250	4.6	C(14)
H(31)	393	561	947	8.2	C(20)
H(32)	411	640	1089	7.3	C(20)
H(33)	410	724	946	5.2	C(20)
H(34)	340	670	553	7.5	N(5)
H(35)	341	629	320	5.7	C(21)
H(36)	307	810	327	5.3	C(21)
H(37)	421	832	342	7.4	C(22)
H(38)	386	918	458	6.9	C(22)
H(39)	452	629	483	8.8	N(6)
H(40)	506	861	586	5.8	C(23)
H(41)	456	910	673	6.5	C(23)
H(42)	538	779	791	6.0	C(24)
H(43)	482	627	771	5.5	C(24)
H(44)	577	636	637	5.0	O(3)

imately 200 terms with *E* greater than 1.80 were used to compute the *E* map from which the position of the chlorine atom was readily found. There were many peaks near $y = 0.25$ and 0.75 and the orientation of the ring system was clear but its exact location in the ap-

parent network of six-membered rings was uncertain. Several trial structures were postulated and checked with Fourier projections down the *b* axis. The initial *R* value of the correct structure was 0.55 for the acridine system alone and 0.30 for a trial structure of the entire molecule deduced from Fourier maps. This structure was refined by block-diagonal least squares isotropically to an *R* value of 0.15 and anisotropically to an *R* value of 0.103. The hydrogen atoms were located from a difference map and their positions were refined isotropically. In the final stages two cycles of anisotropic full-matrix least-squares were calculated for the heavier atoms alone, then two cycles isotropically for the hydrogen atoms alone and then another cycle for the heavier atoms. The final *R* value was 0.066.

The final atomic parameters are listed in Table 1 together with the estimated standard deviations. Those for the heavier atoms were computed from the inverted full matrix and those for the hydrogen atoms were calculated from the diagonal elements of the full matrix when the hydrogen atoms were refined separately. A list of calculated and observed structure factors is given in Table 2.

Computations

Most of the calculations were done on an IBM 1620 computer with programs written in this laboratory [for a list see Johnson (1965*a*) and Gabe, Glusker, Minikin & Patterson (1967)]. Because the memory was not large (20K) the heavy atoms and the hydrogen atoms

Table 2. Observed and calculated structure factors

Each entry lists, in order, h, |F_o| and F_c. Unobserved reflections, a total of 1603, are not included. For the data reduction these were included with one third the estimated intensity which would just have been visible. 569 reflexions in this category had values of F_c greater than |F_o|, 75 had values greater than 2|F_o| and 22 had values greater than 3|F_o|.

Table with columns for h, |F_o|, F_c, and multiple sets of h, |F_o|, F_c. The table contains a large number of rows of numerical data representing structure factors for various reflections.

were refined in separate cycles of block-diagonal least-squares calculations. The scattering factors were taken from *International Table for X-ray Crystallography* (1962) except for hydrogen atoms when the values of Stewart, Davidson & Simpson (1965) were used. The scattering factor for chlorine was corrected for anomalous dispersion with $\Delta f' = 0.3$. The weights in the least-squares calculations were based on counting statistics and instrumental uncertainties. In the final stages of calculation a full-matrix least-squares program, modified by H. L. Carrell from the UCLA program, was run on a CDC 6600 computer at New York University via a DCT 2000 terminal. Again the light and heavy atoms were refined in separate cycles. The program to compute molecular geometry was written by A. Caron and H. L. Carrell and was run on a UNIVAC 1108 computer via a DCT 2000 terminal.

Discussion of the structure

The interatomic distances and interbond angles in the molecule are illustrated in Fig. 1. Torsion angles down

selected bonds in the molecule are shown in Fig. 2. The distances in the acridine moiety are compared with the distances in acridine itself (Phillips, 1956; Phillips, Ahmed & Barnes, 1960; Shefter, 1968) in Table 3. The main difference in ICR 171-OH is the slight lengthening of the bonds designated (*h*), that is the bonds adjacent to the side chain. The first bond from the ring system to a nitrogen atom [C(15)-N(5)] is 1.336 Å which is short and indicates that there is some double bond character present. As shown in Table 4, which is a listing of hydrogen bonds, there is an interaction between N(5) and N(6) of the side chain so that a hydrogen bond, which is not linear (the N(5)-H(34)---N(6) angle is 128°), is formed and the side chain is not an extended zigzag. This is shown in Fig. 3, which was calculated by *ORTEP* (Johnson, 1965*b*).

The sum of the angles around N(6) is 325° (compared with a value of 328.5° for three tetrahedral angles), while that around N(5) is 353° (compared with a value of 360° for a planar arrangement). N(6) is 0.45 Å from the plane through C(23), C(22), H(39) while N(5) is

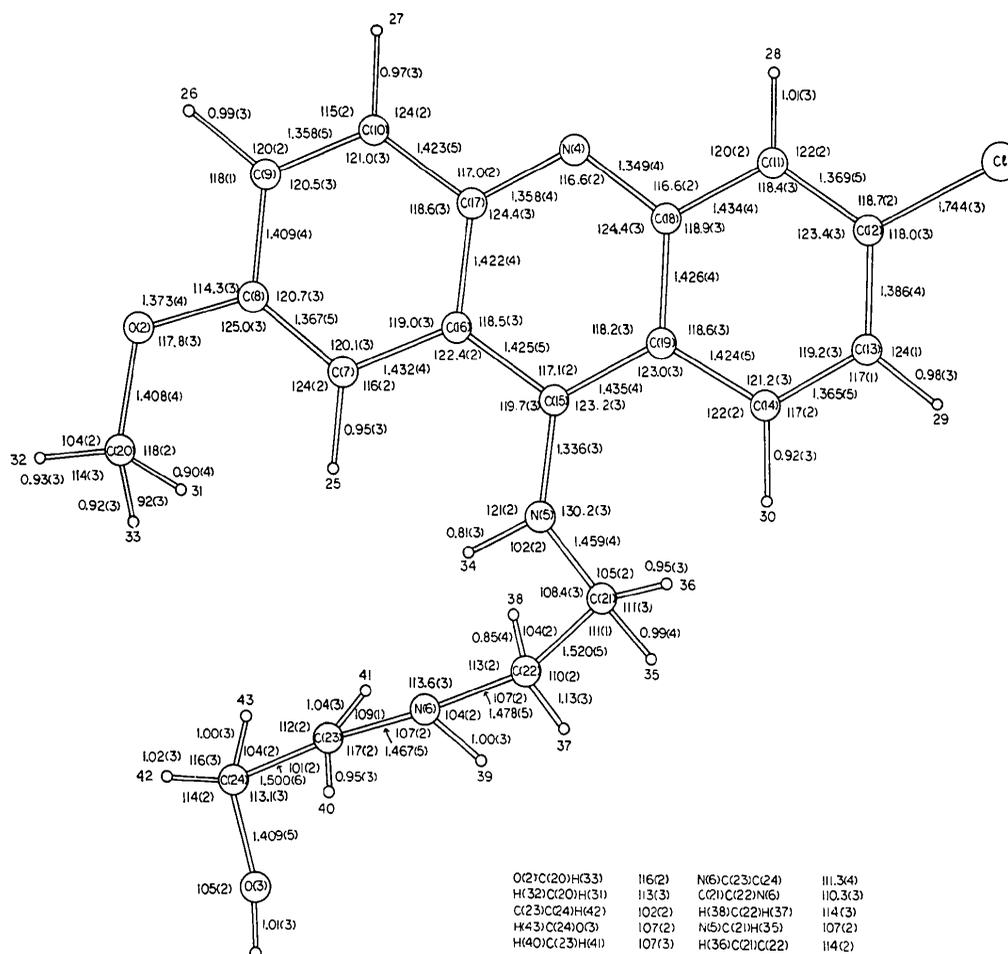


Fig. 1. Interatomic distances and interbond angles.

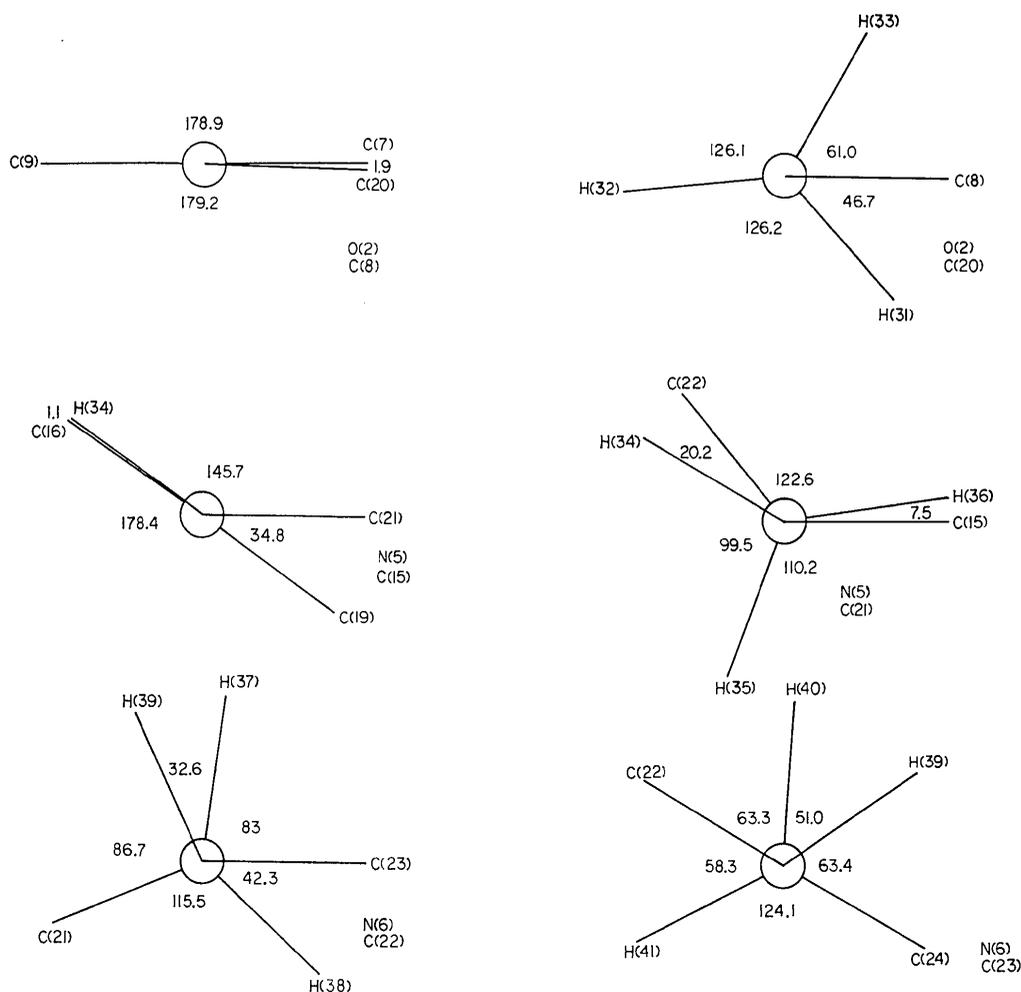


Fig. 2. Torsion angles down certain bonds in the molecule.

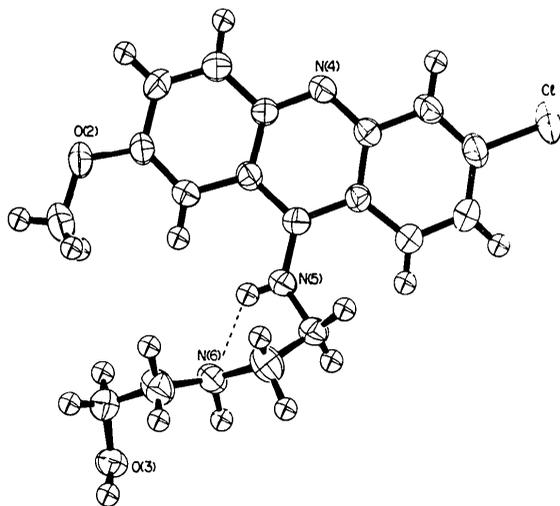


Fig. 3. View of the molecule showing thermal ellipsoids.

0.17 Å from the plane through C(21), C(15), H(34). These results suggest a slight residual positive charge on N(5) and a slight residual negative charge on N(6).

The acridine part of the molecule is not planar and in Fig. 4 an attempt is made to describe this lack of planarity which is probably mainly caused by the lengthening of the bonds C(19)-C(15) and C(15)-C(16) and the planarity of the system C(19), C(15), C(16), N(5). The angle between the planes of the two outer benzene rings in the acridine system is 7.53° but the nonplanarity is not simply a folding about the N(4)-C(15) line. The angle between the plane of the ring containing the methoxy group and that of the central ring is 2.3° while that between the plane of the ring containing the chlorine atom and that of the central ring is 8.1°. The angles between the plane of the central ring and the best planes through N(5)-C(21)-C(22)-N(6) and N(6)-C(23)-C(24)-O(3) are 44.3 and 48.7° respectively with an angle of 87.1° between these last two planes.

Distances and angles concerned with the hydrogen bonding are listed in Table 4 and are illustrated in Fig. 5. The hydrogen bond N(4)---H(44)---O(3), of length 2.80 Å, is the same length as that found for the ring nitrogen atom to a water molecule by Shefter (1968) for an acridine-cytosine-water complex. In the present study the hydrogen bond is to the terminal hydroxyl group of the side chain and may indicate a slight negative charge on N(4). The oxygen of this hydroxyl group also receives a hydrogen bond from a nitrogen atom, N(6), in the side chain. The hydrogen bond to the nitrogen atom of the acridine is similar to the hydrogen bond from a phosphate group to the acridine suggested as a modification of the intercalation model of Lerman (1961) by Pritchard, Blake & Peacocke (1966).

The chlorine atom is surrounded by hydrogen atoms of the $-OCH_3$ and $-O-CH_2-$ groups of other molecules. The system C(9), C(8), O(2), C(20), H(32), Cl forms an extended zigzag with H(32) -0.11 Å and Cl $+1.74$ Å from the plane through the first four atoms.

The packing of the molecule is shown in Fig. 6 which shows the extent of overlap of adjacent ring systems. Nitrogen atoms N(4) and N(5) of different molecules overlap, possibly due to electrostatic attraction as a result of residual charges on these atoms as suggested above. The shortest distances between these rings (one at x, y, z and the other at $\frac{1}{2}-x, \frac{1}{2}+y, 1-z$) are 3.32 Å for N(4)---N(5), 3.49 Å for N(4)---C(21),

3.36 Å for N(5)---C(18), 3.35 Å for C(14)---C(16) and 3.58 Å for C(7)---C(14).

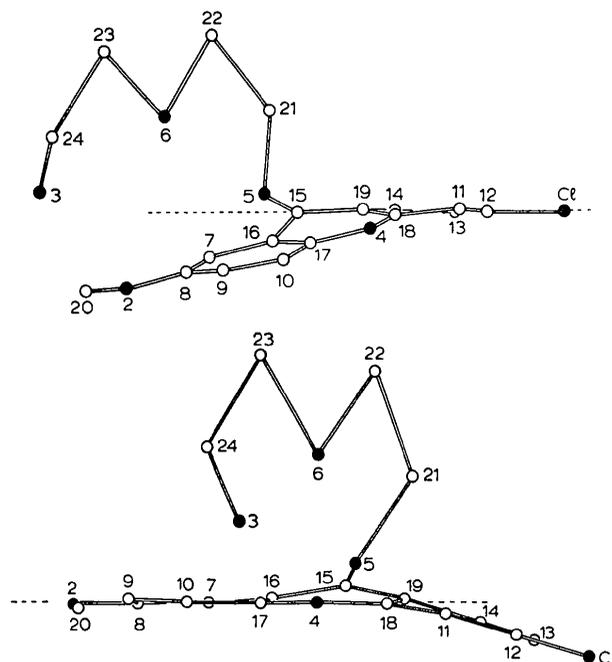


Fig. 4. Extent of buckling of the molecule. Note: the vertical scale is enlarged by a factor of two to show this buckling more clearly.

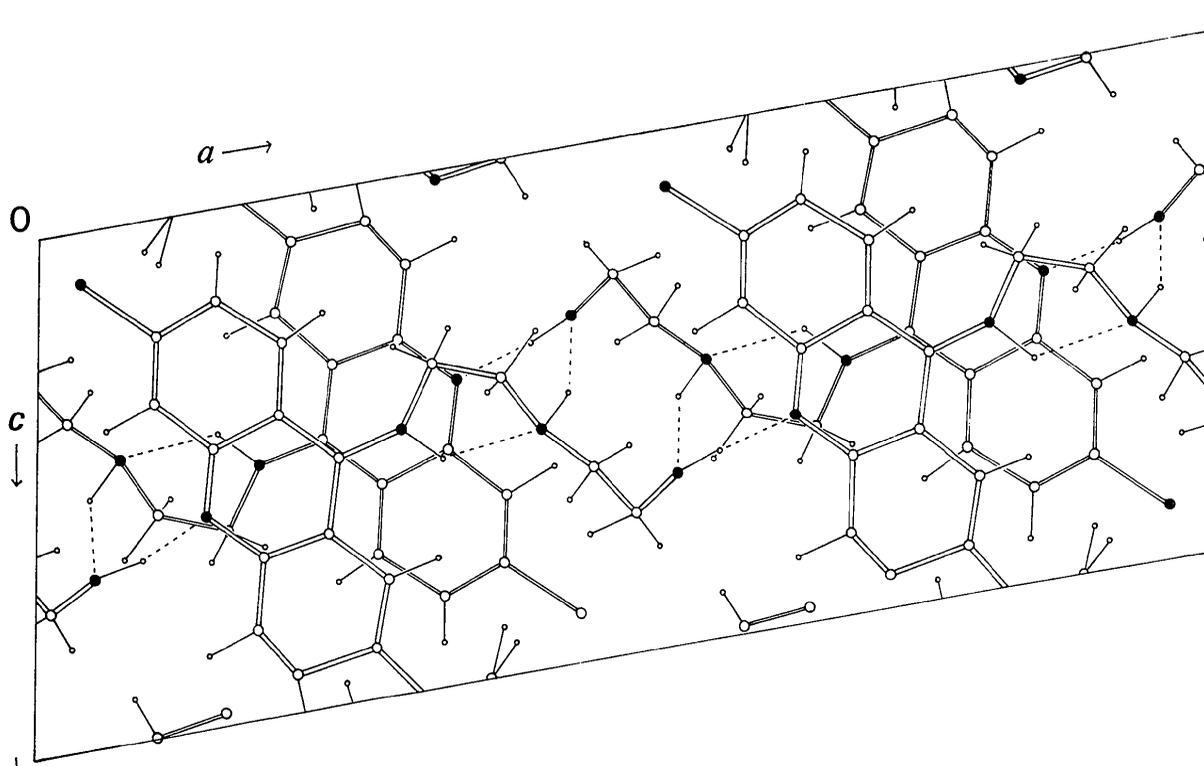


Fig. 5. Projection down the b axis showing the hydrogen bond system.

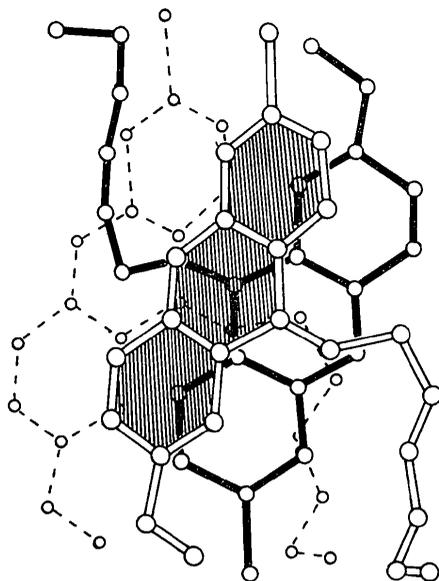


Fig. 6. Overlap of adjacent molecules. The central molecule is denoted by solid black bonds. The view is perpendicular to the least-squares best plane through the acridine part of this molecule.

We thank Drs H. J. Creech, R. Preston and R. Peck for the sample from which crystals were grown. We are grateful to Miss Carol Ann Casciato, Miss Susan E. Cree and Mr Fredric B. Soule for assistance with the data collection and with computing and Dr H. L. Carrell for assistance with computing in the final stages of the refinement.

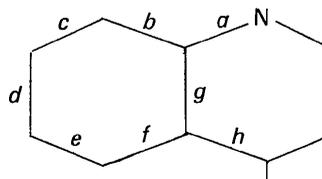
This research was supported by grants CA-10925, CA-06927 and RR-05539 from the National Institutes of Health, U. S. Public Health Service, and by an appropriation from the Commonwealth of Pennsylvania.

References

- GABE, E. J., GLUSKER, J. P., MINKIN, J. A. & PATTERSON, A. L. (1967). *Acta Cryst.* **22**, 366.
International Tables for X-ray Crystallography (1962). Vol. III, pp. 201–246. Birmingham: Kynoch Press.
 JOHNSON, C. K. (1965a). *Acta Cryst.* **18**, 1004.
 JOHNSON, C. K. (1965b). *ORTEP: A Fortran Thermal-Ellipsoid Plot Program for Crystal Structure Illustrations*. ORNL-3794. Oak Ridge National Laboratory, Oak Ridge, Tennessee.
 LERMAN, L. S. (1961). *J. Mol. Biol.* **3**, 18.

Table 3. *A comparison of bond lengths in acridine and in ICR-171-OH*

	Acridine III (Phillips, 1956) e.s.d. 0.006 Å	Acridine II (Phillips <i>et al.</i> 1960)		Acridine- cytosine complex* (Shefter, 1968) (no H)	ICR-171-OH (This work) e.s.d. 0.005 Å
		Molecule 1	Molecule 2		
<i>a</i>	1.342 1.347	1.342 1.345	1.339 1.353	1.378 1.362	1.358 1.349
<i>b</i>	1.428 1.434	1.431 1.424	1.432 1.418	1.426 1.420	1.423 1.434
<i>c</i>	1.369 1.376	1.366 1.362	1.347 1.360	1.415 1.374	1.358 1.369
<i>d</i>	1.415 1.420	1.425 1.436	1.429 1.417	1.438 1.427	1.409† 1.386†
<i>e</i>	1.377 1.364	1.355 1.376	1.348 1.349	1.350 1.351	1.367 1.365
<i>f</i>	1.416 1.435	1.429 1.432	1.427 1.438	1.441 1.450	1.432 1.424
<i>g</i>	1.439 1.425	1.435 1.432	1.431 1.429	1.445 1.452	1.422 1.426
<i>h</i>	1.397 1.382	1.405 1.391	1.386 1.396	1.383 1.409	1.425† 1.435†



* We wish to thank Dr E. Shefter for making his data available to us.
 † Distances marked with † differ from those in the other studies.

Table 4. *Hydrogen bond system*

Donor (<i>D</i>)	Acceptor (<i>A</i>)	Distances (Å)			Angles (°)		
		<i>D</i> ... <i>A</i>	H— <i>D</i>	H... <i>A</i>	<i>D</i> —H... <i>A</i>	<i>A</i> ... <i>D</i> —H	H... <i>A</i> · <i>D</i>
N(5)—H(34)	N(6)	2.72	0.81	2.14	128	38	14
O(3)—H(44)	N(4)	2.80	1.01	1.81	167	9	5
N(6)—H(39)	O(3)	2.94	1.00	2.14	153	18	8

Table 5. Deviations (\AA) of atoms from the best plane through the acridine system

Cl	-0.234	C(7)	-0.054	C(13)	-0.155	C(19)	0.113
O(2)	-0.146	C(8)	-0.092	C(14)	-0.048	C(20)	-0.206
O(3)	0.573	C(9)	-0.052	C(15)	0.183	C(21)	1.141
N(4)	0.066	C(10)	-0.026	C(16)	0.021	C(22)	2.019
N(5)	0.360	C(11)	0.049	C(17)	0.007	C(23)	2.053
N(6)	1.232	C(12)	-0.099	C(18)	0.087	C(24)	1.210

PECK, R. M., PRESTON, R. K. & CREECH, H. J. (1961). *J. Org. Chem.* **26**, 3409.

PHILLIPS, D. C. (1956). *Acta Cryst.* **9**, 237.

PHILLIPS, D. C., AHMED, F. R. & BARNES, W. H. (1960). *Acta Cryst.* **13**, 365.

PRITCHARD, N. J., BLAKE, A. & PEACOCKE, A. R. (1966). *Nature, Lond.* **212**, 1360.

SHEFTER, E. (1968). *Science*, **160**, 1351.

STEWART, R. F., DAVIDSON, E. R. & SIMPSON, W. T. (1965). *J. Chem. Phys.* **42**, 3175.

Acta Cryst. (1972). **B28**, 8

The Molecular Structure of 3β -Acetoxy-20-Hydroxylupane, $C_{32}H_{54}O_3$.*

BY WILLIAM H. WATSON AND HSING-YIE TING

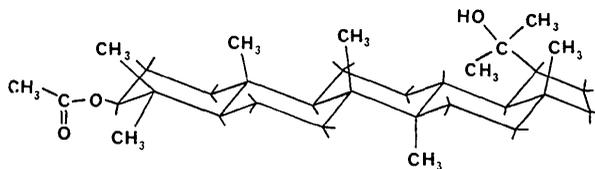
Department of Chemistry, Texas Christian University, Fort Worth, Texas 76129, U.S.A.

AND XORGE A. DOMINGUEZ

Department of Chemistry, Monterrey Institute of Technology, Monterrey, N. L. Mexico

(Received 12 November 1970)

The structure of the monoacetate derivative of lupane- $3\beta,20$ -diol, $C_{32}H_{54}O_3$, was determined by the symbolic-addition procedure and-tangent formula method. The space group is $P2_1$ and cell dimensions are $a=15.198$ (8), $b=8.260$ (7), $c=12.226$ (5) \AA and $\beta=108.6$ (3) $^\circ$. The triterpene lupane- $3\beta,20$ -diol, $C_{30}H_{52}O_2$, was extracted from *Theolocactus bicolor*, and a monoacetate derivative was prepared. The relative molecular configuration was found to be



The molecule is composed of four *trans* fused six-membered rings and one *trans* fused five-membered ring. All six-membered rings are in the chair conformation. The absolute configuration of the 3-position is known, and the absolute configuration of the remainder of the molecule can be established.

Introduction

Cacti from the southwestern region of North America are known to contain alkaloids, terpenes, and a variety of other compounds. Frequently, the materials are isolated in small quantities and conventional means of identification are difficult. A small quantity of a white material was isolated from *Theolocactus bicolor*, and preliminary studies indicated the presence of two hydroxyl groups. An acetate derivative was prepared (m.p. 254–256 $^\circ$ C), and a mass spectrum was obtained. The derivative was assumed to be a diacetate and the formula $C_{29}H_{46-48}O_2$ was proposed for the parent com-

pound. This is an unusual formula for a triterpene, although a few compounds of this type have been reported.

Several crystals of the acetate derivative were supplied to our laboratory by Dr Xorge Dominguez who isolated the compound and made the preliminary studies. The crystals of the acetate derivative occur as colorless elongated parallelepipeds. The proposed formula proved to be in error, and the correct formula and structure were established by single-crystal X-ray diffraction techniques.

Experimental

A crystal of dimensions 1.25 \times 0.35 \times 0.15 mm was mounted with the *b* axis (long dimension) coincident

* Contribution No. 1 from FASTBIOS Laboratory, Texas Christian University.